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Predicting new-onset diabetes after minimally invasive subtotal distal pancreatectomy in benign and borderline malignant lesions of the pancreas

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Abstract

The purpose of this study was to evaluate the time-dependent probability and risk factors of pancreatogenic diabetes mellitus (PDM) in patients who underwent minimally invasive subtotal distal pancreatectomy.

Changes in glucose metabolic consequence of 34 patients (laparoscopic: 31, robotic: 3) who underwent surgery from December 2005 to December 2014 were estimated by assessing impaired fasting glucose, PDM, and PDM-free time analysis.

A total of 22 patients showed glucose intolerance, including 13 (38.2%) with impaired fasting glucose and 9 (26.5%) with PDM. The median onset time of PDM was 6.8 months (range 5.3–13.2 months). The PDM-free time probability according to time interval was 94.1% (6 months), 75.9% (12 months), and 72.6% (18 months). It was shown that body mass index>23 kg/m^2 (49.9 vs 87.9 months, $P=.020$) and preoperative cholesterol >200 mg/dL (40.9 vs 85.2 months, $P=.003$) adversely influenced PDM-free time. Preoperative cholesterol >200 mg/dL (hazard ratio = 6.172; 95% confidence interval, 1.532–24.865; $P=.010$) was significantly associated with short PDM-free time in Cox proportional hazards model.

Patients with high cholesterol levels and high BMI should be closely monitored for the development of PDM.

Abbreviations: BMI = body mass index, DP = distal pancreatectomy, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, MI-STDP = minimally invasive STDP, PDM = pancreatogenic diabetes mellitus, POPF = postoperative pancreatic fistula, PPH = postpancreatectomy hemorrhage, SMV-SV-PV = superior mesenteric vein-splenic vein-portal vein, STDP = subtotal distal pancreatectomy.

Keywords: diabetes mellitus, distal pancreatectomy, subtotal distal pancreatectomy

1. Introduction

When a tumor is detected in the neck or proximal body of the pancreas, surgeons encounter the dilemma of whether to perform central pancreatectomy or distal pancreatectomy (DP) with division of the pancreatic neck, so-called subtotal distal pancreatectomy (STDP). Central pancreatectomy is not frequently performed due to the risk of pancreatic fistula resulting from the 2 cut surfaces created by pancreatectomy, even though its incidence of new-onset pancreatogenic diabetes mellitus (PDM) is lower than that of STDP[1,2]. Therefore, most surgeons choose to perform STDP when the tumor is located in the neck or proximal body of the pancreas. However, removal of approximately 70% of pancreatic parenchyma by dividing the pancreas neck is expected to result in high incidence of postoperative new-onset PDM.

PDM is defined as DM caused by diffuse destruction of the pancreas, such as in pancreatic resection and chronic pancreatitis, leading to deficiency in pancreatic hormones.[3] The American Diabetes Association has categorized PDM as "other specific type of diabetes mellitus-disease of the exocrine pancreas."[4] According to the literature, incidence of new-onset PDM after partial pancreatectomy varies from 4% to 51%,[3,5–9] depending on preexisting diseases, duration of follow-up period, and extent of pancreatic resection. In addition, volume of remnant pancreas after DP varies widely depending on location of tumor and surgical method. Therefore, it is difficult to identify the actual incidence of new-onset PDM after DP.[5,10] In addition, the incidence can vary based on time interval after surgery. Bruijin et al[11] reported, in a systemic review, that within 6 months after surgery, incidence of new-onset PDM was 17%, which increased to 36% after longer follow-up periods.

When performing STDP for benign or borderline pancreatic tumors, a minimally invasive approach is feasible. According to recent literatures, laparoscopic DP with or without splenectomy has been accepted as a safe and effective treatment option for

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benign, borderline malignant, and even malignant pancreatic tumors.[12–14] We recently described our technique of minimally invasive STDP (MI-STDP),[15–17] and have been accumulating long-term follow-up data. As incidence of new-onset PDM may vary according to resected volume of the pancreas, we only enrolled patients who underwent MI-STDP with the same percentage of resected volume. We evaluated the overall incidence of new-onset PDM and changes in glucose metabolic consequence while focusing on the time interval after surgery. This study can provide insight into long-term consequences to glucose metabolism in patients with long life expectancies after undergoing MI-STDP for benign and borderline tumors.

2. Materials and methods

2.1. Patient selection

From December 2005 to December 2014, medical records of patients who underwent MI-STDP (laparoscopic or robotic) by dividing the neck of pancreas for benign or borderline tumors of pancreas were retrospectively reviewed. As remnant volume and percentage of the pancreas may vary in conventional DP according to resected portion of pancreas, we excluded patients who underwent DP less than a total neck, body, and tail resection were performed. As open STDP was performed in most malignant tumors and differences of surgical insults between open and minimally invasive procedure might influence glucose impairment after surgery, patients who underwent open STDP were excluded. Patients who had preoperative diagnosis of DM were also excluded. Over the study period, a total of 43 patients underwent MI-STDP. Except for 9 patients who had diabetes before surgery, 34 patients were included in this study. During the first 2 years after STDP, patients were regularly examined every 3 months, and then twice a year thereafter. Five years after operation, patients were tested once a year. This retrospective study was approved by the Institutional Review Board of Yonsei University College of Medicine.

2.2. Clinicopathological characteristics

This study evaluated perioperative clinicopathological variables and follow-up data including the following: age, sex, body mass index (BMI), tumor size, pathologic diagnosis, complications such as postoperative pancreatic fistula (POPF)[18] and post-pancreatectomy hemorrhage (PPH),[19] 90-day mortality, length of hospital stay, estimated blood loss, transfusion, fasting serum albumin, cholesterol, glucose level, and HbA1c.

2.3. Definition of glucose metabolic consequences

Impaired fasting glucose (IFG) was defined as a fasting serum glucose level of 100 to 125 mg/dL. Impaired glucose tolerance (IGT) was not assessed in this retrospective study, as oral glucose tolerance test was not administered to patients. According to the American Diabetes Association criteria for diagnosis of DM,[4] newly developed PDM after surgery was defined when 2 consecutive follow-up blood laboratory tests fulfilled the following criteria: fasting (no caloric intake for at least 8 h) serum glucose ≥126 mg/dl, HbA1c >6.5%, or classic symptoms of hyperglycemia or hyperglycemic crisis and a random serum glucose ≥200 mg/dL. As the probability of PDM changes are based on the period of time after surgery, PDM-free time after surgery was estimated by the Kaplan–Meier method.

2.4. Surgical technique

We have described our technique for MI-STDP in previous studies.[15–17] In brief, the whole pancreas is exposed after the division of gastrocolic ligament, and a portion of pancreatic neck is carefully dissected from the superior mesenteric vein-splenic vein-portal vein (SMV-SV-PV) confluence to create a window for the division of pancreatic neck. Based on the tumor characteristics, small individual tributary vessels were either preserved for splenic vessel-conserving spleen-preserving STDP, or the entire segments of both splenic vessels were excised with distal pancreas for splenic vessel-sacrificing spleen-preserving STDP. In cases where spleen conservation was difficult, combined splenectomy was performed.

2.5. Statistics

Continuous variables were described as mean ± standard deviation, and categorical variables were described as frequency (%). In comparative analysis, Student t test and χ^2 test were applied. PDM-free time was calculated using the Kaplan–Meier method, and significant difference between groups was assessed with a log-rank test. Subsequently, Cox proportional hazards model was applied for multivariate analysis to detect clinicopathological factors predictive of impaired PDM-free time. Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL). P values $<.05$ were considered to be statistically significant.

3. Results

3.1. Patient demographics

The average age of patients was 48 ± 14 years. Twenty-eight patients were female and 6 were male. Radiologic tumor size was 3.6 ± 2.1 cm in maximal diameter, and pathological diagnoses are listed in Table 1. Thirty patients (88.2%) either retained their spleens by splenic vessels-conserving method (20, 58.8%), or underwent segmental resection by splenic vessels method (10, 29.4%). Operation time was 265 ± 111 minutes, and intraoperative blood loss was estimated to be 240 ± 237 mL. Only 1 patient required intraoperative transfusion. Seven patients (20.6%) developed grade B POPF, and 1 patient (2.9%) experienced grade C PPH requiring reoperation. PPH developed when the closed suction drain was removed on postoperative day 7. Metallic clip was released from the vessel when drain was removed because the surgical metallic clip was inserted into side hole of the drain. Length of hospital stay was found to be 9 ± 5 days. There was no 90-day mortality. Mean duration of follow-up after surgery was 40.3 months (range 3.0–97.1 months).

Table 1

Pathologic diagnosis of the patients.

Diagnosis	Frequency (%)
Solid pseudopapillary tumor	9 (26.5)
Mucinous cystic neoplasm	7 (20.6)
Intraductal papillary mucinous neoplasm	6 (17.6)
Chronic pancreatitis/pseudocyst	5 (14.7)
Pancreatic neuroendocrine tumor	4 (11.8)
Serous cystic neoplasm	3 (8.8)

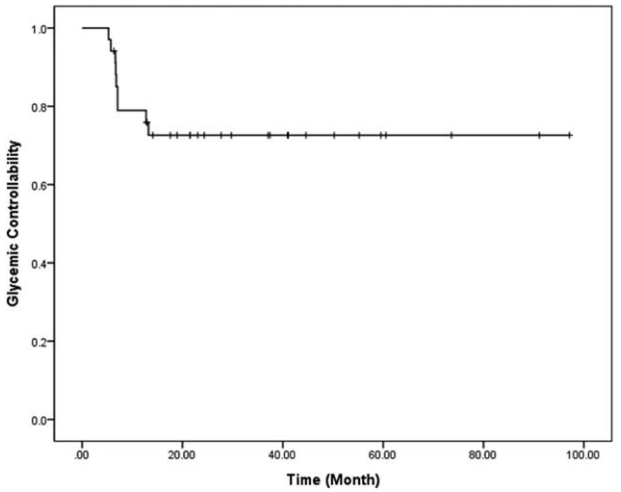

Figure 1. PDM-free time rate after MI-STDP. PDM-free time rates according to time interval after surgery were 94.1% (6 months), 75.9% (12 months), and 72.6% (18 months).

3.2. Changes in glucose metabolic consequences following MI-STDP

Preoperative serum fasting glucose concentration was observed to be 91 ± 8 mg/dL. During the last follow-up period, final postoperative fasting glucose was found to be 113.1 mL/dL, which was significantly higher than preoperative fasting glucose level ($P = .001$). During the follow-up period, a total of 22 patients (64.7%) showed glucose intolerance, including 13 (38.2%) with IFG and 9 (26.5%) with PDM. All 9 patients developed PDM within 24 months after surgery with a median onset time of 6.8 months (range 5.3–13.2 months). PDM-free time rates according to time interval after surgery were 94.1% (6 months), 75.9% (12 months), and 72.6% (18 months) (Fig. 1).

3.3. Clinicopathological factors influencing PDM-free time

It was shown that BMI >23 kg/m^2 (49.9 vs 87.9 months, $P = .020$) and preoperative cholesterol >200 mg/dL (40.9 vs 85.2 months, $P = .003$) adversely influenced PDM-free time over the follow-up period (Table 2; Fig. 2). In particular, among 19 patients with both BMI ≤23 kg/m^2 and preoperative serum cholesterol ≤200 mg/dL, almost all of the patients (18 patients, 94.8%) were observed to be PDM-free (follow-up duration: mean, 33.3 months with range, 6.3–97.1 months). For these patients, last follow-up fasting serum glucose was 99 ± 10 mg/dL and HbA1c was 5.8 ± 0.2%.

Age >45 years (57.9 vs 90.1 months, $P = .057$) and chronic pancreatitis/pseudocyst (14.9 vs 77.8 months, $P = .063$) were marginally associated with shorter PDM-free time after MI-STDP. However, other clinicopathological characteristics such as sex, tumor size, surgical approach (laparoscopic vs robotic, spleen preservation vs resection), preoperative fasting serum glucose, operation time, and postoperative POPF were not associated with PDM-free time after STDP ($P > .05$; Table 2).

3.4. Preoperative serum cholesterol >200 mg/dL as independent predictive factor for short PDM-free time

Cox proportional hazards model showed that preoperative cholesterol >200 mg/dL (hazard ratio = 6.172; 95% confidence interval, 1.532–24.865; $P = .010$) was significantly associated with short PDM-free time after MI-STDP (Table 2). Older patients (58 ± 7 vs 45 ± 14, $P = .001$) and those with high BMI (25.3 ± 4.0 vs 22.9 ± 2.7, $P = .045$) were statistically associated with preoperative serum cholesterol >200 mg/dL (Table 3).

Table 2

PDM-free time analysis after MI-STDP according to clinicopathologic characteristics.

	Univariate analysis*		Multivariate analysis†		
Variables (n)	PDM-free time (mean), mo	*P*	HR	95% confidential interval	*P*
Age, y		.057			
≤45 (13)	90.1				
>45 (21)	57.9				
Sex		.570			
Female (28)	70.6				
Male (6)	62.4				
BMI, kg/m^2		.020			.162
≤23 (20)	87.9				
>23 (14)	49.9		3.263	0.621–17.145	
Glucose (preop), mg/dL		.520			
≤90 (18)	72.0				
>90 (16)	67.6				
Cholesterol (preop), mg/dL		.003			.010
≤200 (24)	85.2				
>200 (10)	40.9		6.172	1.532–24.865	
Chronic pancreatitis/pseudocyst		.063			
Yes (5)	14.9				
No (29)	77.8				
Tumor size, cm		.237			
≤3.6 (22)	65.9				
>3.6 (12)	52.1				
Surgical mode		.679			
Laparoscopic (31)	73.4				
Robotic (3)	39.0				
Spleen-preservation		.807			
No (4)	71.7				
Yes (30)	72.9				
POPF		.283			
No (27)	76.5				
Yes (7)	37.5				

BMI = body mass index, HR = hazards ratio, MI-STDP = minimally invasive subtotal distal pancreatectomy, PDM = pancreatogenic diabetes mellitus, POPF = postoperative pancreatic fistula, Preop = preoperative.

* Kaplan–Meier analysis.

† Cox proportional hazards model.

4. Discussion

This study aimed to assess the overall percentage of new-onset PDM and PDM-free time rate after MI-STDP, as well as to evaluate the risk factors influencing PDM-free time. It has been known that estimates of new-onset PDM after partial pancreatectomy vary from 4% to 51%, since the incidence of PDM is influenced by many factors such as the portion of pancreas resected, total resected volume, duration of follow-up, and preexisting diseases.[3,5–9]

When we focused on left-sided resection of the pancreas, the resected volume had a wide range. If the resection margin was located at the pancreas neck, which is known as STDP, the resected volume could be >70%. Although incidences of new-onset PDM after DP were reported to have wide range, no existing study has yet investigated the incidence of new-onset

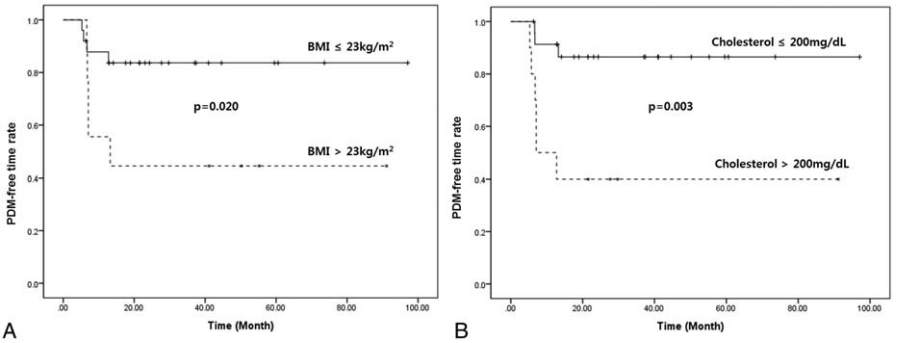

Figure 2. Influence of BMI and cholesterol level on PDM-free time. BMI >23 kg/m^2 (49.9 vs 87.9 months, $P = .020$) and preoperative cholesterol >200 mg/dL (40.9 vs 85.2 months, $P = .003$) adversely influenced PDM-free time rate during follow-up period.

PDM limited to STDP. Sakata et al[20] reported that resection of >80% of the pancreas resulted in development of PDM in approximately 67% of patients, and all patients developed new-onset PDM if >90% of the pancreas was resected. Kang et al[21] reported that endocrine functional impairment was 73.3% in patients who underwent resection of >50% in volume of the pancreas. In the present study, for STDP that had between 70% and 80% resected volume of the pancreas, the incidence of new-onset glucose impairment, including IFG and PDM, after STDP was 64.7% (IFG: 38.2%, PDM: 26.5%). Our result of investigating PDM after STDP did not show higher incidence of PDM compared with conventional DP used in other studies.

Although resected volume of the pancreas in the development of new-onset PDM is important, identification of the underlying disease is also important. In the systemic review by De Bruijin et al,[11] the average cumulative incidence of new-onset PDM after DP was higher in patients who underwent DP for chronic pancreatitis than for benign or (potentially) malignant lesions (39% vs 14%, $P < .000$). In this study, the incidence of new-onset PDM in chronic pancreatitis/pseudocyst was higher than non-chronic pancreatitis conditions (60% vs 20.7%, $P = .102$, data was not shown). However, no statistically difference was observed. In PDM-free time analysis, chronic pancreatitis/pseudocyst (14.9 vs 77.8 months, $P = .063$) were marginally associated with shorter PDM-free time after MI-STDP (Table 2).

As the rates of developing PDM after pancreatic resection can vary according to time interval after pancreatectomy, a cross-sectional assessment for incidence of PDM may fail to provide enough information. Therefore, this study assessed PDM-free time analysis using the Kaplan–Meier method and Cox proportional hazards model. In this study, all 9 patients who developed PDM did so within 24 months after surgery with a median onset time of 6.8 months (range 5.3–13.2 months). PDM-free time was sustained until a mean of 72.7 month after STDP, and 5-year serum glucose control was determined to be 72.6%. Shirakawa et al[22] reported that the median onset time of PDM after DP was 8 months (range 0.5–42 months). However, Kwon et al[7] reported that the mean time interval of PDM after surgery was 16.8 months. In their study, all types of pancreatic resections, including DP, central pancreatectomy, pylorus-preserving pancreaticoduodenectomy (PPPD), and pancreaticoduodenectomy (PD), were included. Median-onset time of PDM after surgery may be earlier in left-sided pancreatic resection than in PD or PPPD. Pancreatic beta cells are concentrated in body and tail of the pancreas. Therefore, left-sided pancreatic resection may particularly predispose patients to develop PDM. In PD or PPPD, remnant pancreas which is anastomosed with the jejunum or stomach might develop atrophic changes. These morphologic changes could result in later-onset PDM in patients who underwent PD or PPPD, compared with those who underwent left-sided pancreatectomy.

Table 3

Clinical characteristics of patients with preoperative serum cholesterol >200 mg/dL.

	Preoperative serum cholesterol, mg/dL		
	≤200	>200	*P*
Sex (female/male), n	19/5	9/1	.644
Age, y	45 ± 14	58 ± 7	.001
Preoperative serum glucose, mg/dL	91 ± 9	91 ± 8	.934
Body mass index, kg/m^2	22.9 ± 2.7	25.3 ± 4.0	.045
Diagnosis (non-CP/CP), n	21/3	8/2	.618
Tumor size, cm	3.8 ± 2.4	3.1 ± 0.9	.273

Variables are expressed as the mean ± standard deviation. CP = chronic pancreatitis, Non-CP = non-chronic pancreatitis.

It is very important to identify the risk factors for PDM after pancreatectomy, as these can influence the decision regarding but the interval and length of follow-up for patients with benign and borderline tumors with long life expectancy. IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL, high cholesterol, and hypertension.[4] In this study, it was shown that BMI >23 kg/m^2 and preoperative cholesterol >200 mg/dL adversely influenced PDM-free time during follow-up period, and that preoperative serum cholesterol >200 mg/dL was significantly associated with short PDM-free time after MI-STDP in multivariate analysis (Table 2; Fig. 2).

A euglycemic patient with obesity might develop overt DM after pancreatic resection due to preoperative insulin resistance and relative insulin deficiency.[3] In studies of Korean populations, BMI cutoff values of >20 kg/m^2[21] and 23.5 kg/m^2[7] have been suggested as predictive of endocrine impairment after pancreatic resection. In western countries, obesity is defined as BMI >30 kg/m^2. However, the International Association for the Study of Obesity (IASO) and the International Obesity Task Force (IOTF) have proposed a BMI cutoff value of 25 kg/m^2 for obesity and 23 to 24.9 kg/m^2 for being overweight in Asian populations.[23] Our result showed that BMI >23 kg/m^2 had an adverse influence on the incidence of PDM during follow-up period, and that patients with high BMI (25.3 ± 4.0 vs 22.9 ± 2.7,

$P = .045$) were statistically associated with preoperative serum cholesterol >200 mg/dL (Table 3).

In summary, when a tumor is located near the neck of the pancreas, STDP offers the maximal extent of resection. When preservation of a significant amount of pancreatic volume is impossible, surgeons should consider the risk of PDM before surgery. Patients with high BMI and high cholesterol levels, with benign and borderline malignant lesions of the pancreas, should be closely monitored for development of PDM over a long period of time.

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